II. REMARKS

Formal Matters

Claims 1-41 are pending after entry of the amendments set forth herein.

Claims 1-38 were examined. Claims 1-35 were rejected. Claims 36-38 were withdrawn from consideration.

Claims 1, 3, 4, 6, 7, 13, 15, 17, 20, 22-24, 26, 29, 31, and 33 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 13, 20, and 29 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 6, lines 12-13; Example 1. The amendments to claims 3, 4, 6, 7, 13, 15, 17, 22-24, 26, 31, and 33 are merely editorial in nature. Accordingly, no new matter is added by these amendments.

Please replace claims 1, 3, 4, 6, 7, 13, 15, 17, 20, 22-24, 26, 29, 31, and 33 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Obviousness-type double patenting

Claims 1-5 and 20-25 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-8 of U.S. Patent No. 5,667,968.

Enclosed is a terminal disclaimer, disclaiming patent term beyond the expiration date of U.S. Patent No. 5,667,968. Thus, the rejection of claims 1-5 and 20-25 under obviousness-type double patenting may be withdrawn.

Rejection under 35 U.S.C.§101/§112, first paragraph

Claims 1-35 were rejected under 35 U.S.C.§101 as allegedly lacking utility. Claims 1-35 were rejected under 35 U.S.C.§112, first paragraph as allegedly not enabled.

Rejection under 35 U.S.C.§101

The Office Action stated that while the specification asserts a specific and substantial utility, "preventing degeneration of retinal neurons caused by exposure to light or other environmental trauma" is not credible. Applicants respectfully traverse the rejection.

The Office Action stated that even normal aging results in the death of neurons, which cannot be prevented from naturally degenerating, and therefore "preventing degeneration of retinal neurons" is not credible. However, if one adopted such logic, any preventive measure lacks credibility, since all mammals ultimately die. Yet preventive medicine is well accepted as credible in the medical community.

Furthermore, as shown in the Example, administration of certain neurotrophic factors before exposure to light resulted in a high degree of photoreceptor rescue when animals were exposed to light. Thus, the neurotrophic factors prevented the degree of damage that would have occurred but for the administration of the neurotrophic factor. Accordingly, preventing degeneration of retinal degeneration caused by exposure to light or other environmental trauma is a credible utility.

Nevertheless, and solely in the interest of expediting prosecution, claims 1, 13, 20, and 29 are amended to recite a method for "reducing degeneration."

Rejection under 35 U.S.C.§112, first paragraph

The Office Action stated that since the claimed invention is not supported by either a credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicants respectfully traverse the rejection.

As discussed above, claims 1-35 are indeed supported by a credible asserted utility. Accordingly, those skilled in the art would know how to use the claimed invention.

Applicants submit that the rejections of claims 1-35 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-35 were rejected under 35 U.S.C.§112, first paragraph, as allegedly not enabled.

The Office Action stated that the specification does not provide enablement for any method for "reducing" or "preventing" neurodegeneration of retinal neurons generically with structurally uncharacterized modified neurotrophic factors orally, subcutaneously, intravenously, or intramuscularly. Applicants respectfully traverse the rejection.

The Office Action stated that the specification is enabling for a method of reducing degeneration of the outer segment of photoreceptor cells following intraocular or systemic administration of neurotrophic factors BDNF, CNTF, NT-3, aFGF, bFGF, IL-1β, TNF-α, and IGF-2.

Neurotrophic factors

The Office Action stated that the specification proposes a method of reducing or preventing degeneration of retinal neurons in a patient with a therapeutically effective dose of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1β, TNG-α and IGF-2. The Office Action further stated that no significant results were obtained for NGF, NT-3, EGF, PDNF, insulin, IGF-I, and IL-6.

First, the claims as amended recite administration of a neurotrophic factor effective to reduce retinal degeneration. Thus, the claims specifically exclude neurotrophic factors that are not effective to reduce retinal degeneration. As stated in the MPEP §2164.08(b), the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments would be inoperative or operative with expenditure of no more effort than is normally required in the art[1]. The specification provides a description of how to determine whether a given neurotrophic factor reduces retinal cell degeneration. Specification, page 10, lines 15-21; and Example 1. Thus, those skilled in the art could readily test whether any factor reduces retinal cell degeneration.

The Office Action acknowledged that eight different factors were effective in reducing degeneration of the outer segment of photoreceptor cells. Those skilled in the art would reasonably expect that other neurotrophic factors would also reduce degeneration of retinal neurons.

Indeed, others have described reduction in retinal neuron degeneration, using the methods of the instant invention. The following references describe reduction of degeneration of retinal neurons,

comprising administering neurotrophic factors other than the neurotrophic factors specifically shown in the Example section of the instant application as effective in reducing retinal neuron degeneration:

1) Machida et al. (2001) *Invest. Ophthamol. Vis. Sci.* 42:1087-1095; Exhibit 1
   Machida discusses reduction of photoreceptor degeneration by administering lens epithelium-derived growth factor (LEDGF).
2) Cao et al. (2001) *Invest. Ophthamol. Vis. Sci.* 42:1646-1652; Exhibit 2
   Cao discusses reduction of photoreceptor degeneration by administering pigment epithelium-derived factor (PEDF).
3) Sanftner et al. (2001) *Mol. Ther.* 4:622-629; Exhibit 3
   Sanfter discusses reduction of photoreceptor degeneration by delivering glial cell line derived neurotrophic factor (GDNF).
4) Lau et al. (2000) *Invest. Ophthamol. Vis. Sci.* 41:3622-3633; Exhibit 4
   Lau discusses reduction of photoreceptor degeneration by delivering fibroblast growth factor-2 (FGF-2).
5) Koeberle and Ball (2002) *Neurosci.* 110:555-567; Exhibit 5
   Koeberle and Ball discuss rescue of retinal ganglion cells by administering neurturin.

As is apparent from the above sampling of recent literature, those skilled in the art, using the methods of the instant invention as claimed, were able to administer various neurotrophic factors, in addition to those specifically shown by Applicants in a working example, in amounts effective to reduce degeneration of retinal neurons.

The Office Action stated that no "significant" results were obtained for NGF, NT-3, EGF, PDGF, insulin, IGF-1, and IL-6. Applicants note for the record that the Office Action stated that the instant specification is enabling for a method involving administering NT-3. Furthermore, the specification states that some degree of rescue of photoreceptors was observed with heparin, PDGF, NGF, EGF, and IGF-1. Specification, page 14, lines 29-30; Figures 1 and 2. The claims require that retinal cell degeneration be reduced by administration of a neurotrophic factor. If degeneration is reduced to <u>any</u> degree, then use of the neurotrophic factor is encompassed by the claim.

[1] Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)

The Office Action further stated that the specification does not provide structural characteristics, and provides little functional characteristics, for how to make the neurotrophic factors required to practice the claimed method, and stated that the specification fails to define what specific amino acids are critical for any neurotrophic-related function. However, there is no statutory requirement that Applicants define what specific amino acids are critical for any neurotrophic-related function. The claims recite administration of a neurotrophic factor effective to reduce retinal cell degeneration. The specification describes how to determine whether a given neurotrophic factor reduces retinal cell degeneration. Methods for preparing fragments of a neurotrophic factor are well known and routine in the art. Methods for generating derivatives and analogs of neurotrophic factors are well known and routine in the art. Those skilled in the art routinely prepare and test large numbers of fragments, derivatives, and analogs of proteins such as neurotrophic factors. Once such a fragment, derivative, or analog is made, it is also a routine matter, given the guidance in the specification and the knowledge in the art, to test such factors. Indeed, the references discussed above provide further evidence for the fact that those skilled in the art could test various neurotrophic factors for efficacy in reducing degeneration of retinal neurons. Thus, those skilled in the art, given the guidance in the specification, could readily determine whether any given neurotrophic factor, including fragments, derivatives, and analogs, would be effective to reduce retinal cell degeneration.

Route of administration

The Office Action stated that the specification is enabling for intraocular or systemic administration of certain neurotrophic factors, and stated that the specification is not enabling for reducing neurodegeneration of retinal neurons with neurotrophic factors orally, subcutaneously, intravenously, or intramuscularly. Applicants respectfully traverse the rejection.

The Office Action has acknowledged that the specification is enabling for intraocular and systemic administration of certain neurotrophic factors. It follows that oral, subcutaneous, intravenous, and intramuscular administration are also enabled.

Retinal neurons

The specification states that the invention provides methods for reducing degeneration of various retinal cells, including photoreceptors, retinal ganglion cells, displaced retinal ganglion cells, amacrine cells, displaced amacrine cells, and horizontal and bipolar neurons. Specification, page 7, lines 16-21.

Applicants have provided working examples of reduction of degeneration of photoreceptors. Example 1. Those skilled in the art would reasonably expect that the instant methods as claimed are effective to reduce degeneration of retinal neurons in addition to photoreceptors.

The fact that those skilled in the art would reasonably expect that the instant methods as claimed are effective to reduce degeneration of retinal neurons is corroborated by the following references:

1) Peterson et al. (2000) *J. Neurosci.* 20:4081-4090; Exhibit 6
   Peterson et al. states that CNTF enhances survival of retinal ganglion and photoreceptor cells exposed to otherwise lethal perturbation.
2) Kido et al. (2000) *Brain Res.* 884:59-67; Exhibit 7
   Kido et al. discuss the ability of BDNF to protect inner retinal cells, retinal ganglion cells, and amacrine cells from N-methyl-D-aspartate-induced neuronal death.
3) Chen and Weber (2001) *Invest. Ophthamol. Vis. Sci.* 42:966-974; Exhibit 8
   Chen and Weber discuss the ability of BDNF to enhance retinal ganglion cell survival.
4) Schmeer et al. (2002) *Eur. J. Neurosci.* 15:637-643; Exhibit 9
   Schmeer et al. discusses the ability of GDNF to enhance retinal ganglion cell survival.

Thus, the instant methods as claimed are enabling for methods of reducing degeneration of retinal neurons.

Therapeutically effective dose

The Office Action stated that it is unknown what parameters are required to be assayed in order to determine when or if the instant invention is therapeutically effective in treating any pathological condition. However, the claims recite "reducing degeneration of retinal neurons." Retinopathies and other pathological conditions wherein retinal degeneration occurs, such as those recited in claim 21, are well known in the art. Those in the field, including, e.g., medical personnel who examine patients with retinopathies, are well aware of parameters that one would use to determine whether retinal degeneration is reduced. As stated in the MPEP §2164.05(a), the specification need not disclose what is well known

to those skilled in the art, and preferably omits that which is well known to those skilled and already available to the public.

The Office Action stated that in order to practice the full scope of the invention, regeneration of the damaged axons in the neurodegenerative disease states is required. However, regeneration is not required. All that is required is that degeneration of retinal neurons is reduced. Applicants have provided ample evidence that retinal neuron degeneration is reduced when neurotrophic factors that are effective in reducing retinal degeneration are administered.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-35 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1-35 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that no recitation is included that defines when "reducing or preventing degeneration of retinal neurons" is accomplished, or what constitutes a "therapeutically effective dose." Applicants respectfully traverse the rejection.

Without conceding as to the correctness of this rejection, claims 1, 13, 20, and 29 are amended to recite administering a dose of a neurotrophic factor "effective to reduce degeneration of retinal neurons, wherein degeneration of retinal neurons is reduced."

Applicants submit that the rejection of claims 1-35 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL250CON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 9, 2002

By: _____
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\UCAL\250con4\resp 02-13-02 OA.doc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendments to claims 1, 3, 4, 6, 7, 13, 15, 17, 20, 22-24, 26, 29, 31, and 33, as shown below.

1. (Amended) A method of reducing [or preventing] degeneration of retinal neurons in a mammal caused by exposure to light to other environmental trauma comprising administering to the mammal, prior to, during or following such exposure, a [therapeutically effective] dose of a neurotrophic factor effective to reduce degeneration of retinal neurons, wherein degeneration of retinal neurons is reduced.

3. (Amended) The method of claim 1 [2] wherein said retinal neurons are photoreceptors.

4. (Amended) The method of claim 1 [3] wherein said administration is intraocular.

6. (Amended) The method of claim 1 [3] wherein said administration is systemic delivery.

7. (Amended) The method of claim 6 wherein said neurotrophic factor has been modified [in such a way as] to increase its ability to be transported across the blood-retinal barrier.

13. (Amended) A method of [preventing or] reducing degeneration of retinal neurons in a mammal caused by exposure to light or other environmental trauma comprising administering to the mammal, prior to, during or following said exposure, a [therapeutically effective] dose of one or more factors selected from the group consisting of acidic fibroblast growth factor (aFGF), bFGF plus heparin, aFGF plus heparin, interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), wherein said dose is effective to reduce degeneration of retinal neurons, and wherein degeneration of retinal neurons is reduced.

15. (Amended) The method of claim 13 [14] wherein said administration is intraocular.

17. (Amended) The method of claim 13 [14] wherein said administration is delivered systemically.

20. (Amended) A method of reducing [or preventing] degeneration of retinal neurons in a mammal having a pathological condition wherein retinal degeneration occurs, comprising administering to said mammal a [therapeutically effective] dose of a neurotrophic factor effective to reduce degeneration of retinal neurons, wherein degeneration of retinal neurons is reduced.

22. (Amended) The method of claim 20 [21] wherein said neurotrophic factor is brain derived neurotrophic factor, ciliary neurotrophic factor, neuorotrophin-3 or a combination thereof.

23. (Amended) The method of claim 20 [22] wherein said retinal neurons are photoreceptors.

24. (Amended) The method of claim 20 [23] wherein said administration is intraocular.

26. (Amended) The method of claim 20 [23] wherein said administration is by systemic delivery.

29. (Amended) A method of reducing [or preventing] degeneration of retinal neurons in a mammal having a pathological condition wherein retinal degeneration occurs, comprising administering to said mammal a [therapeutically effective] dose of one or more factors selected from the group consisting of acidic fibroblast growth factor (aFGF), bFGF plus heparin, aFGF plus heparin, IL-1β, TNF-α and IGF-2, wherein said dose is effective to reduce degeneration of retinal neurons in the mammal, and wherein degeneration of retinal neurons is reduced.

31. (Amended) The method of claim 29 [30] wherein said administration is intraocular.

33. (Amended) The method of claim 29 [30] wherein said administration is systemic delivery.